REMARKS

Claims 1-24 were pending in this application. Claims 10-16 and 18 have been withdrawn from consideration as being drawn to a nonelected invention. The nonelected claims are being maintained of record, pending rejoinder and/or the filing of one or more divisional applications. By this Amendment, claims 1, 17, 20-22 and 24 have been amended, and claims 2 and 6-9 have been canceled. Accordingly, the claims now pending and under examination are claims 1, 3-5, 17 and 19-24.

The claims have been amended to recite that the virus is a vesicular stomatitis virus (VSV). Support for this amendment may be found, *inter alia,* in original claim 9. This amendment overcomes all of the anticipation rejections and most of the grounds of the enablement rejection. Applicants' evidence and arguments overcoming the remaining grounds of the enablement rejection appear below.

Claims 20 and 21 have been amended to overcome the Section 112, second paragraph rejection. Support for the amendment of claims 20 and 21 can be found in paragraphs [0051] and [0050], respectively.

The specification was objected to because of the handwriting appearing on the first line of page 3, which was not in compliance with 37 CFR 1.52(a)(1)(iv). The specification has been amended to correct this informality. Support for the amended paragraph may be found in the original paragraph including its handwritten portion.

Applicants respectfully submit that the amendments are fully supported by the disclosure and do not raise an issue of new matter. Entry of the amendments is respectfully requested.

CLAIM FOR PRIORITY

On November 19, 2003 applicants timely amended the specification to contain a specific reference to the prior applications. On page 2 of the Action the November 19, 2003 Amendment is acknowledged. Yet on page 3 the Action mentions the requirement for an application to contain a specific reference to the prior applications whose benefit is desired. It is believed that the subject application is in compliance with the formal requirements for entitlement to the benefit of the prior applications. If the Examiner believes otherwise, applicants respectfully request that the alleged deficiency be clearly identified.

ELECTION OF SPECIES

In response to the election of species requirement, applicants hereby confirm their March 18, 2005 telephonic election of replication-competent VSV.

CLAIMS SATISFY SECTION 112, SECOND PARAGRAPH

Claims 20 and 21 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The claims were rejected based on alleged ambiguity concerning where and to what the chemotherapeutic agent and interferon are administered. In response the claims have been amended to further clarify that the chemotherapeutic agent (claim 20) or the interferon (claim 21) is administered to the mixture recited in claim 1.

INVENTION IS ENABLED

Claims 1-8, 17 and 19-24 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly not being enabled by the specification. This rejection is respectfully traversed.

The Office has taken the position that the specification does not enable the *ex vivo* killing by replication-competent VSV of all types of neoplastic cells, only acute myelogenous leukemia (AML). The Office has also taken the position that the specification does not enable the use of VSV in the presence of an interferon. Both positions are wrong.

The rejection has wrongly taken the position that the specification does not enable the *ex vivo* killing by replication-competent VSV of neoplastic cells generally, only AML. In doing so, the Office has improperly sought to place on applicants the burden of proving that the invention works. Thus the rejection states:

> "However, the specification does not provide sufficient evidences supporting that any or all viruses can selectively kill any neoplastic cells over [] autologous or allogenic isolated normal hematopoietic cells in the presence of an interferon treatment. . . . The specification even does not provide sufficient evidence[] to support that other neoplasm rather than myeloge[n]ous leukemia will be selective killed by VSV in the mixture ex vivo sample, such as a breast cancer induced by Rb or BRCA-2 gene expression."

(March 31, 2005 Office Action, paragraphs 19-20) (underlining added).

Contrary to the clear implication of the rejection, applicants are not required to submit experimental results demonstrating the anti-tumor activity of vesicular stomatitis virus. Rather, the Office bears the burden of establishing that the specification does not satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. As stated by the CCPA in In re Marzocchi:

> "As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the

> statements contained therein which must be relied on for enabling support."

In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, ___ (underlining added). It is not sufficient for the Office to simply assert that it doubts the correctness of the statements in the disclosure. The Office must back up its doubts with evidence or reasoning. Again from In re Marzocchi:

> "In any event, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement."

In re Marzocchi, 439 F.2d at 224, 169 USPQ at ___ (internal citations omitted) (underlining added). No adequate evidence or reasoning has been cited in support of the rejection. To the contrary, the demonstrated success in a variety of tumor cell lines supports applicants' position that the invention works for its intended purpose.

All or virtually all neoplastic cells can be reduced or eliminated in accordance with the method of this invention. In addition to the specification, ample data from other sources also supports the claim that tumor cells are, in general, appropriate targets for therapy with VSV. The demonstrated antitumor activity of VSV in a wide variety of tumor cell types is summarized in the following table:

Diverse Cancers Besides Acute Myelogenous Leukemia (AML) That Are Killed by VSV.

Type of cancer sensitive to VSV	Cell Line(s)	Reference
Ovarian Carcinoma	A2780, OVCA 420, C13	Specification Example 3. The title of this example indicates that these cancer cells are killed by VSV. Furthermore, paragraph [0029] indicates that: "As another example, diverse tumor cell types were shown to be sensitive to VSV including ovarian carcinoma, fibrosarcoma, melanoma, prostate carcinoma, and leukemia cells (see Example 3)."
	Six lines	Stojdl DF et al., 2003. Cancer Cell 4:263-275.
Lung carcinoma	LC80	Specification Example 3
	Various	Stojdl DF et al., 2003. Cancer Cell 4:263-275.
Melanoma	SK-MEL-3	Specification Example 3. Also, in vitro killing of SK-MEL-3 melanoma cells by VSV is further indicated by Bell et al, WO 01/19380, Example 23. Additionally, in vivo antitumor activity of VSV against SK-MEL-3 indicated by Bell et al, WO 01/19380, Examples 16, 18, and 25
	Various	Stojdl DF et al., 2003. Cancer Cell 4:263-275.
	B16(F10)	Fernandez et al., 2002, J Virol 76:895-904
Hepatocellular carcinoma	Hep 3B, Hep G2	Ebert et al., 2003, Cancer Res 63:3605-11
Breast carcinoma	4T1	Ebert et al., 2005, Cancer Gene Ther 12:350-8
	Various	Stojdl DF et al., 2003. Cancer Cell 4:263-275
	TSA	Porosnicu et al., 2003, Cancer Res 63:8366-76
Prostate carcinoma	LNCAP	Specification Example 3. Also, in vitro killing of LNCAP prostate cancer cells by VSV is further indicated by Bell et al, WO 01/19380, Example 20
	LNCAP	Ahmed et al., 2004, Virology 330:34-9
	2 lines	Stojdl DF et al., 2003. Cancer Cell 4:263-275
Glioblastoma	C6	Balachandran S et al., 2001 J Virol 75:3474-79

	U87	Duntsch et al., 2004, J Neurosurg 100:1049-59
Colon carcinoma	HCT116	Specification Example 3
	Various	Stojdl DF et al., 2003. Cancer Cell 4:263-275.
Renal carcinoma	Various	Stojdl DF et al., 2003. Cancer Cell 4:263-275.
Lymphoma	EL4	Porosnicu et al., 2003, Cancer Res 63:8366-76
Megakaryocytic Leukemia	MO7E	Bell et al, WO 01/19380, Example 2: "Two leukemia cell lines MO7E and L1210; Table 1) were killed following an overnight infection and produced large amounts of virus."
Lymphoid Leukemia	L1210	As noted above.
Chronic Myelogenous Leukemia	K-562	Bell et al, WO 01/19380, Example 19
		Porosnicu et al., 2003, Cancer Res 63:8366-76
T Cell Leukemia	MOLT-4	Bell et al, WO 01/19380, Example 19
Myeloma	SR	Bell et al, WO 01/19380, Example 19
	H929	Bell et al, WO 01/19380, Example 19
	8226/Dox40	Porosnicu et al., 2003, Cancer Res 63:8366-76

Copies of the publications cited in the preceding table are enclosed herewith. As seen from the evidence set forth in the specification and confirmed by a review of the scientific literature, VSV can be used successfully to reduce or eliminate neoplastic cells in an *ex vivo* mixture of normal, hematopoietic cells and neoplastic cells by contacting said mixture with VSV. The evidence demonstrates that applicants' teaching is true for such mixtures containing neoplastic cells generally and is not limited to AML.

In addition, the rejection has wrongly taken the position that the specification does not enable the use of VSV in the presence of an interferon. Example 3 reports the results of an experiment measuring the ability of VSV to grow in a variety of normal and neoplastic cell lines, both untreated or pre-treated with alpha-interferon. "Pretreatment of the normal cell cultures with interferon reduced viral production to <1000 infectious virus particles per ml., while tumor cell lines continued to produce copious amounts of virus particles (105-108 plaque forming units per ml.)." (Example 3, paragraph [0055]; and See

Table 2.) (underlining added). These results demonstrate that VSV is able to replicate in interferon-treated tumor cells.

In view of the foregoing, applicants respectfully submit that the claimed invention is enabled in accordance with the requirements of Section 112, first paragraph. Withdrawal of the enablement rejection is respectfully requested.

DOUBLE PATENTING

Claims 1-2 and 6-9 have been provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 35 of copending Application No. 09/664,444, claim 18 of copending Application No. 10/743,639, and claim 18 of copending Application No. 10/743,649, in all three cases in view of Weber et al. and Rummel et al.

In response, applicants will consider filing a terminal disclaimer when otherwise allowable subject matter is indicated.

CLAIMED INVENTION IS NOVEL

Claims 1, 2, 4, 5, 17 and 24 have been rejected under 35 U.S.C. §102 as allegedly being anticipated by Belch, et al. Claims 1, 4, 5 and 17 have been rejected under 35 U.S.C. §102 as allegedly being anticipated by Seth, et al. Claims 1, 4, 5 and 17 have been rejected under 35 U.S.C. §102 as allegedly being anticipated by Marini, et al. Claims 1-5, 17, 19, 20 and 22-24 have been rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Morris, et al., (A) U.S. Patent Publication No. 2001/0048919A1. Claims 1-5, 17, 19, 20 and 22-24 have been rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Morris, et al., (B) U.S. Patent Publication No. 2001/0048919A1 (It is believed that paragraph 48 of the Office Action contains a clerical error and that U.S.

Patent Publication No. 2002/0006398 was intended to be identified as Morris, et al. (B)). All of these rejections are respectfully traversed.

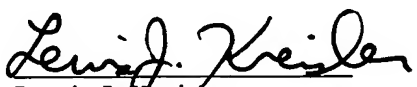
The claims relate to the use of vesicular stomatitis virus to reduce or eliminate neoplastic cells in an *ex vivo* mixture of normal hematopoietic cells and neoplastic cells. None of the references disclose the use of VSV for this purpose. Rather, they are cited as allegedly teaching *ex vivo* purging regimens using different viruses, namely reovirus (Belch, et al.; Morris, et al. (A); Morris, et al. (B)) or adenovirus (Seth, et al.; Marini, et al.). Accordingly, none of the references discloses the claimed invention.

CONCLUSION

In view of the amendments and the preceding remarks, it is believed that all of the objections and rejections have been overcome. Reconsideration and withdrawal of all objections and rejections is respectfully requested.

It is believed that no fee is required in connection with the filing of this Amendment. If any fee is required, the Commissioner is hereby authorized to charge the amount of such fee to Deposit Account No. 50-1677.

Respectfully submitted,



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Enclosures